UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

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MEMORANDUM

DATE: July 27, 2000

SUBJECT: **Terrazole (Etridiazole):** HIARC Revisit to Estimate the Percentage (%) Dermal Absorption of the Fungicide, Terrazole.

FROM: Michelle M. Centra
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THROUGH: Jess Rowland, Co-Chair
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Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Danette Drew, Risk Assessor
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PC Code: 084701

On April 27, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base, selected doses and endpoints for acute dietary as well as occupational exposure risk assessment, reassessed the Reference Dose, and addressed the sensitivity of infants and children from exposure to the fungicide, terrazole (Memorandum: M. Centra, J. Rowland, P. Wagner, April 27, 1999).

At this meeting, the HIARC recommended that a default value of 100% be used for dermal absorption in the terrazole risk assessment because: (1) there were no dermal absorption studies available in the terrazole toxicology database, (2) the two dermal toxicity studies conducted in rabbits (one study using terrazole technical and the second study using the Terraclor Super X formulation as the test material) were classified as unacceptable-guideline studies and are therefore, not adequate for regulatory purposes and (3) the acidic nature of terrazole technical (pH 3-4 in water) could cause considerable dermal irritation and would most likely breach the skin barrier.

Uniroyal Chemical Company, Inc., has recently submitted a rat dermal absorption study conducted in 1985 to address the issue of dermal absorption. Evaluation of this study by the Health Effects Division's Science Analysis Branch identified deficiencies that resulted in a nonguideline study classification. In spite of the study deficiencies, the reviewer estimated a dermal absorption factor of 15%, but suggested that these results be used with caution. The Registrant's summary of this study acknowledged the deficiencies and estimated a wide range (7-28%) for the dermal absorption of terrazole.

On July 18, 2000, the HIARC met to determine whether the dermal absorption study is adequate for risk assessment and, if so, could a percentage (%) dermal absorption be estimated for this fungicide.
The HIARC concluded that the results of this study could not be used for deriving a dermal absorption factor that could be used for risk assessment based upon the following factors: (I) significant loss of compound can occur with highly volatile chemicals during preparation of the dosing material, during application of the material to the test animal, during the exposure period, at termination, and during sample collection. (Loss during preparation and application of the material will result in under-dosing. Loss during the exposure period will result in an unbalanced pattern of dose distribution and incomplete recovery.)

The HIARC agreed that such losses occurred in the case of terrazole. The actual dose to which the rats were exposed in this study cannot be satisfactorily estimated due to the high volatility of the chemical. Additionally, the skin injury observed during the study could potentially be more severe than was reported due to the acidic nature of the chemical coupled with the under-dosing of the animals (Terrazole was shown to volatilize during preparation and dosing). The HIARC concluded that the data reported in this study are not adequate for use in evaluating the potential dermal absorption in humans following exposure to terrazole and therefore, the study is unacceptable for regulatory purposes.

Consequently, the Committee re-affirmed its earlier decision to use the default value of 100% dermal absorption (i.e oral equivalent).

In addition, the following toxicity studies are required by the HIARC:

1. A dermal absorption study in rats since terrazole is classified as a B_2 Carcinogen and requires a dermal cancer risk assessment. This study would provide a dermal absorption factor which then could be used in such an assessment in place of the default value (100%).

2. A 21-day dermal toxicity study in rats that assesses all of the parameters required in the testing guidelines for the 90-day dermal toxicity study (870.3250). This subchronic study would provide toxicology endpoints for non-cancer occupational/residential dermal risk assessments.

2. An inhalation toxicity study conducted in rats for 28 days that assesses all of the parameters required in the testing guidelines for the 90-day inhalation toxicity study (This

study should be conducted in accordance with the testing guidelines for the 90-day inhalation toxicity study (870.3465) with the exception that the exposure duration be limited to 28 days). This study is required because the exposure estimates for terrazole indicate that exposure via the inhalation route is of greater concern than that via the dermal route. This subchronic study would provide toxicology endpoints for non-cancer occupational/residential inhalation risk assessments.